Oxygen treatment for acute severe asthma

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Deaths from asthma in England and Wales dropped by about 6% a year in people aged 5-64 from 1983 to 1995,[1] but about 20 children and 1600 adults still die in the United Kingdom every year from acute asthma. Profound hypoxaemia may be a readily preventable cause of some of these deaths. The British Thoracic Society's asthma guidelines advise oxygen as first line treatment in hospital for all patients in cases of acute severe asthma.[2] However, the guidelines do not advise treatment with oxygen in primary care in children and do not insist on its use in adults. The recent death of a child in a primary care setting after administration of salbutamol nebulised with air prompted us to question whether treatment with oxygen should be recommended in all cases of acute severe asthma, including those presenting in primary care.

Summary points

- Asthma causes 1600 deaths in the United Kingdom every year
- Progressive hypoxaemia is probably an important cause of death
- Oxygen should be the first treatment given to any patient with acute severe asthma
- Nebulisation of β_2 agonists with air during severe attacks may worsen hypoxaemia
- Patients with acute severe asthma should receive β_2 agonists nebulised with oxygen

Methods

A systematic review was not possible as there have never been any randomised controlled trials of oxygen in acute severe asthma. We therefore present a traditional literature review and our opinion based on it. We selected 24 publications from our personal collections and from Medline searches. Using the search terms "asthma" *and* "hypoxaemia *or* hypoxemia *or* hypoxia *or* oxygen" *and* "salbutamol *or* albuterol" yielded 204 papers, of which 11 were included in this review. The other 13 papers that we evaluated were from our personal collections.

Results and discussion

In acute severe asthma, narrowing of the airway occurs as a result of bronchospasm, mucosal oedema, and hypersecretion. The homoeostatic response to this is to decrease blood flow to underventilated lung units, thus maximising oxygenation by matching pulmonary perfusion with alveolar ventilation. This was shown in an elegant series of studies spanning nearly two decades that used the multiple inert gas technique to study ventilation-perfusion relations and gas exchange in asthmatic patients with varying degrees of disease severity.[3–5] The pattern of ventilation-perfusion is bimodal in acute severe asthma, ranging from normally perfused areas to areas of hypoxic pulmonary vasoconstriction. However, the percentage of cardiac output to areas with a low ventilation-perfusion ratio increases with worsening severity of the acute flare, ranging from 0.4% in chronic stable asthma to 28-36% in the most severe acute flares,[5 6] including those requiring mechanical ventilation.

Treatment with inhaled β_2 agonists is often given to relieve bronchospasm and improve oxygenation. In acute severe asthma, nebulisation of β_2 agonists without oxygen can cause or worsen hypoxaemia. The mechanism for this has been understood since 1967, when it was shown that isoprenaline, a β agonist then in common use for asthma, when nebulised with compressed air resulted in pulmonary vasodilatation, increasing perfusion to poorly ventilated lung units and ventilation-perfusion mismatch, and thus worsening hypoxaemia.[7] Since then it has been found that salbutamol can also worsen ventilation-perfusion mismatch by causing pulmonary vasodilatation and increasing cardiac output.[8]

Findings in children

The first report of such effects in children was in 1969, when a significant fall in arterial blood oxygen saturation was found in asthmatic children after they inhaled salbutamol, even though this improved forced expiratory volume in one second in the same period.[9] A later study recorded a fall in arterial oxygen saturation of more than 5% in nine out of 18 asthmatic children aged 2-15 years who were treated with salbutamol nebulised with air.[10] A small randomised crossover study failed to show a significant decrease in oxygenation during nebulisation with air in 27 episodes of acute severe asthma; however, in 10 cases arterial oxygen saturation decreased by 2-6%, with the biggest drops occurring 10-15 minutes after nebulisation.[11] More

recently, in a study of 111 children with acute severe asthma, six children with pneumonic consolidation in addition to asthma who were treated with salbutamol nebulised with oxygen became profoundly hypoxaemic when oxygen was discontinued after nebulisation.[12] Taken together, these studies provide strong evidence that a small number of children develop important hypoxaemia related to salbutamol administration during acute episodes of asthma if the drug is administered without oxygen.

Findings in adults

The findings in children contrast with those in adults. Over the past 30 years many studies have assessed the effects of salbutamol on oxygenation in asthmatic adults, either as a primary or secondary end point.[3 8 13–18] Most of these studies were small, uncontrolled, and of widely varying design, and some had conflicting results. Most published data show that salbutamol does not have a clinically important effect on oxygenation in asthmatic adults. This seems to be true for both stable and acute asthma, across a range of doses administered by various routes. However, the studies are limited by their exclusion of the most severe exacerbations, particularly those accompanied by marked hypoxaemia.[18] Even though the average change in oxygenation in response to salbutamol in these studies may not be significant, the fact that considerable variability exists among patients has ramifications for those in extremis. In 1974 Choo-Kang postulated that this variability might be due to variations between patients in the response of vascular smooth muscle to stimulation of β_2 adrenoceptors,[18] and it is now known that polymorphism of the β_2 adrenoceptor gene is an important inheritable determinant of smooth muscle response to agonists in the airway.[19]

Deaths from asthma

Most asthma deaths occur in the community, often in patients whose symptoms have been poorly controlled for days or even weeks before the fatal attack.[20] Two hypotheses have been postulated for the cause of these deaths. Firstly, cardiac arrhythmias may contribute to some of the observed mortality, particularly in adults. The risk of arrhythmia is theoretically greatly increased by hypokalaemia and prolongation of the QTc interval, both well described side effects of β_2 agonists and theophyllines.[21] However, in a series of admissions of patients whose asthma attacks were nearly fatal, few arrhythmias other than sinus tachycardias and bradycardias were documented.[22]

A far more likely hypothesis is that deaths occur as a result of hypoxaemia.[22] As the forced expiratory volume in one second falls below 25% of predicted (or peak expiratory flow rate is $<30\%$ of predicted), progressively worsening hypoxaemia occurs secondarily to ventilation-perfusion mismatch and alveolar hypoventilation.[23] Giving air driven, high dose nebulised salbutamol to genetically susceptible patients at this point may transiently increase ventilation-perfusion mismatch sufficiently to cause a further critical acute desaturation.

The British Thoracic Society's asthma guidelines advise oxygen as first line treatment in hospital for all patients in cases of acute severe asthma. Ideally oxygen should be given before and concurrently with a nebulised bronchodilator to maximise alveolar oxygenation in areas of poor ventilation and should then be continued after nebulisation.[2]

Features of severe asthma	Features of life threatening asthma
Age 1-5 years	**Age 1-5 years**
• Tachycardia	• Cyanosis
• Flaring	• Silent chest
• Use of accessory muscles	• Fatigue
• Recession	• Reduced level of consciousness
• Head retraction	**Age >5 years**
• Inability to feed	• Cyanosis
Age >5 years	• Inability to speak
• Tachycardia	• Silent chest
• Use of accessory muscles	• Fatigue
• Recession	• Reduced level of consciousness
• Peak expiratory flow $<50\%$ of best	• Peak expiratory flow $<33\%$ of best

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The guidelines for treatment of acute severe asthma in general practice imply that general practitioners should be prepared to treat acute asthma of all severities but do not advise the use of oxygen for children or insist on its use in adults. This may be because many general practices do not keep an oxygen cylinder, relying instead on air driven nebulisers or metered dose inhalers and holding chambers. The use of metered dose inhalers and holding chambers rather than nebulisers for drug delivery was reviewed recently by the Cochrane Collaboration, which concluded that outcomes were similar whatever the method of drug delivery and that spacers may even have some advantages in children. However, these recommendations were not intended for drug delivery in life threatening asthma.[24]

It is impossible to prove that the continuing trickle of deaths from asthma in Britain is a result of hypoxaemia caused by air driven nebulisers. Many factors may contribute to hypoxaemia in these patients, including bacterial pneumonia, previous poor control, extreme bronchospasm, and mucus plugging. The important point is that asthmatic patients are still dying during acute attacks—and the use of oxygen before, during, and after nebulised β_2 agonist therapy in primary care and in the community is rational and could save lives. Refillable portable oxygen cylinders are readily available and can be used to drive nebulisers if they are fitted with high flow valves. Oxygen is also useful in many other medical emergencies. As long as resources, training, and safety procedures are adequate, oxygen should be available in every general practice. Patients with severe disease could be provided with oxygen cylinders with high flow valves for emergency use at home. This is already the practice in some units that deal with patients with difficult asthma.

Caveats

There are two important caveats to our suggestion. Firstly, whether oxygen should be available for home visits requires careful consideration, including a risk-benefit analysis. This would be best done by the British Thoracic Society in conjunction with primary care colleagues when the guidelines are next updated. Secondly, administration of oxygen is clearly beneficial in children and young adults with asthma; however,

patients over 45 with a history of chronic obstructive pulmonary disease should receive salbutamol nebulised with air to avoid carbon dioxide narcosis.

Conclusion

Treatment of mild and moderate asthma attacks should continue as at present, with either air driven nebulisers or metered dose inhalers and holding chambers. This should not cause hypoxaemia. However, if the signs of a severe or life threatening attack are present (see box), oxygen before and after treatment with a β_2 agonist nebulised with oxygen should be the standard treatment wherever the patient happens to be. We urge the British Thoracic Society to review this issue when it updates its guidelines.

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Laudanum in Lakeland

Among the Christmas reading in our family last year was *A Passionate Sisterhood* by Kathleen Jones. This carefully researched book begins with the young lives of the two sets of sisters—the Frickers and the Hutchinsons—that Coleridge, Wordsworth, and Southey married into, and with Wordsworth's own sister, Dorothy. Then, in its later chapters, Coleridge's daughter Sara and Wordsworth's daughter Dora, together with Southey's daughters, take centre stage.

More may often be learnt about the medicine of earlier times from lay people than from what their doctors wrote about it. The lay sources are more vivid and impartial in describing the treatments offered and their effects. Nowhere can this be truer than in the rich documentation left by the Lakeland poets, their extended families, and their wide acquaintanceship; and what it reveals about their dependency on opiates is astonishing to modern eyes. Some, for instance Coleridge's daughter Sara and the "opium eater" De Quincey, were franker about their addiction than others; but the extent to which all resorted to laudanum goes a long way to explain the invalidism, insomnia, bowel complaints, and failed pregnancies that ran through their lives. Here, just one brief quotation must suffice to illustrate this. It comprises three verses of "Poppies" from *Pretty Lessons in Verse* written by Sara Coleridge for children and, in particular, for her son Herbert.

The poppies blooming all around
My Herbert loves to see,
Some pearly white, some dark as night,
Some red as cramasie …

When poor mama long restless lies
She drinks the poppy's juice;
That liquor soon can close her eyes
And slumber soft produce.
O' then my sweet my happy boy
Will thank the poppy flow'r
Which brings the sleep to dear mama
At midnight's darksome hour.

Kathleen Jones' book, meant primarily to display the lives and talents of the Lakeland sisterhood, also serves to show how prevalent was the use of laudanum in the nineteenth century, as a remedy for every complaint from toothache to the pain of advanced malignancy. Its side effects did not go unrecognised, but there were no good alternatives and it afforded rapid relief. Whether it fed or impaired imaginations as fertile as Coleridge's can only be speculated on, but its influence on any of the writers who regularly took it can not be ignored. Nor, presumably, was the literary circle of the Lakeland poets out of the ordinary in their use of the drug, except in the amount of written testimony they left about its effects. Two centuries later, at least as far as "respectable" society is concerned, we probably live in a less, not a more, drug dependent age than they did.

The Passionate Sisterhood was published by Constable in 1997 but is unaccountably out of print. Copies are still obtainable from good bookshops.

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